PATENT COOPERATION TRE[illegible]Y

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
MXI-301CPPC		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/027044	28/07/2005	30/07/2004
Applicant		
CELLDEX THERAPEUTICS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

VACCINE CONJUGATES COMPRISING A MONOCLONAL ANTIBODY BINDING TO HUMAN DENTRITIC CELLS AND BETA HUMAN CHRONIC GONADOTROPIN

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/027044

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. type of material

   [X] a sequence listing

   [ ] table(s) related to the sequence listing

   b. format of material

   [X] on paper

   [X] in electronic form

   c. time of filing/furnishing

   [X] contained in the international application as filed

   [ ] filed together with the international application in electronic form

   [X] furnished subsequently to this Authority for the purpose of search

2. [X] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/027044

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61K39/395 A61P37/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data, PAJ, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HE L-Z ET AL: "A Novel Human Cancer Vaccine Elicits Cellular Responses to the Tumor-Associated Antigen, Human Chorionic Gonadotropin [beta]" CLINICAL CANCER RESEARCH 15 MAR 2004 UNITED STATES, vol. 10, no. 6, 15 March 2004 (2004-03-15), pages 1920-1927, XP002393832 ISSN: 1078-0432 the whole document ----- -/--	1-45

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2006	29/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Le Flao, K

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HE LIZHEN ET AL: "An antigen presenting cell-targeted cancer vaccine that elicits CD4 and CD8 effector responses to the hCGbeta tumor-associated antigen." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 44, July 2003 (2003-07), page 167, XP001208026 & 94TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH; WASHINGTON, DC, USA; JULY 11-14, 2003 ISSN: 0197-016X abstract	1-45
A	RAMAKRISHNA V ET AL: "Mannose receptor targeting of tumor antigen pmel17 to human dendritic cells directs anti-melanoma T cell responses via multiple HLA molecules" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 172, no. 5, 1 March 2004 (2004-03-01), pages 2845-2852, XP002376446 ISSN: 0022-1767 abstract	1-45
A	WO 03/040169 A (MEDAREX, INC; DEO, YASHWANT, M; KELER, TIBOR) 15 May 2003 (2003-05-15) examples 1,2	1-45
A	FRLETA D ET AL: "Class II-targeted antigen is superior to CD40-targeted antigen at stimulating humoral responses in vivo." INTERNATIONAL IMMUNOPHARMACOLOGY. FEB 2001, vol. 1, no. 2, February 2001 (2001-02), pages 265-275, XP002394474 ISSN: 1567-5769 the whole document	1-45
P,X	RAMAKRISHNA VENKY ET AL: "Synergistic role of TLR Agonists in T cell-mediated immunity induced by mannose receptor antibody targeting of tumor antigens to human DCs" JOURNAL OF IMMUNOTHERAPY, vol. 28, no. 6, November 2005 (2005-11), page 658, XP008067471 & 20TH ANNUAL SCIENTIFIC MEETING OF THE INTERNATIONAL-SOCIETY-FOR-BIOLO GICAL-THERAPY-OF-CANCER; ALEXANDRIA, VA, USA; NOVEMBER 10 -13, 2005 ISSN: 1524-9557 abstract	1-45

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/027044

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 41-*45 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/027044

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03040169 A	15-05-2003	CA 2466049 A1	15-05-2003
		CN 1612934 A	04-05-2005
		EP 1448787 A2	25-08-2004
		JP 2006501131 T	12-01-2006
		MX PA04004324 A	16-05-2005

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/027044	28.07.2005	30.07.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/48 A61K39/395 A61P37/04

Applicant
CELLDEX THERAPEUTICS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Le Flao, K Telephone No. +31 70 340-1040

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/027044

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in electronic form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 41-45

because:

☒ the said international application, or the said claims Nos. 41-45 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30, 32, 33, 35, 36, 38 and 40-45
	No:	Claims	31,34,37,39
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-45
Industrial applicability (IA)	Yes:	Claims	1-40
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Claims 41-45 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reference is made to the following documents:

D1: HE L-Z ET AL: "A Novel Human Cancer Vaccine Elicits Cellular Responses to the Tumor-Associated Antigen, Human Chorionic Gonadotropin [beta]" CLINICAL CANCER RESEARCH 15 MAR 2004, vol. 10, no. 6, pages 1920-1927, XP002393832

D2: HE LIZHEN ET AL: "An antigen presenting cell-targeted cancer vaccine that elicits CD4 and CD8 effector responses to the hCGbeta tumor-associated antigen." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 44, July 2003, page 167, XP001208026

D3: RAMAKRISHNA V ET AL: "Mannose receptor targeting of tumor antigen pmel17 to human dendritic cells directs anti-melanoma T cell responses via multiple HLA molecules" JOURNAL OF IMMUNOLOGY, vol. 172, no. 5, 1 March 2004, pages 2845-2852, XP002376446

D4: WO 03/040169 A (MEDAREX, INC; DEO, Y M; KELER, T) 15 May 2003

D5: FRLETA D ET AL: "Class II-targeted antigen is superior to CD40-targeted antigen at stimulating humoral responses in vivo." INTERNATIONAL IMMUNO-PHARMACOLOGY. FEB 2001, vol. 1, no. 2, pages 265-275, XP002394474

D1 discloses the generation of B11-hCG beta conjugate with covalent link, B11 being a human anti dendritic cells (DC) binding to human mannose receptor. B11ScFv-hCG beta is also disclosed (see the whole document).

D2 discloses monocyte-derived DC pulsed with B11-hCG beta eliciting potent cytolytic and proliferative T cell responses, including killing or hCG beta-expressing cancer cell lines (see the whole document).

D3 discloses B11-pmel 17 fusion protein, pmel 17 being a human tumor antigen (abstract). D4 discloses the generation of B11 antibody, its ScFv fragment and B11-pmel 17 vaccine conjugate. D5 discloses the interest of targeting antibodies to CD40 expressed on APCs (abstract).

NOVELTY

Claims 31, 34, 37 and 39 are not novel over D1 which discloses DCs exposed to B11-hCG beta in the presence of CD40L (p.1922, left-hand column, §2) and their use for inducing a T-cell immune response (p.1924, right-hand column, §2).

None of the cited document discloses a conjugate comprising a monoclonal antibody binding to human APCs linked to hCG beta and to an immunostimulatory agent or a method of immunizing a subject. Claims 1-30, 32, 33, 35, 36, 38 and 40-45 are therefore novel.

INVENTIVE STEP

Claim 1 differs from D1, closest prior art, by the fact the molecular conjugate comprises in addition to the monoclonal antibody binding to human APCs linked to hCG beta disclosed in D1, an immunostimulatory agent.

No effect has been shown to be associated with the difference: the examples of the present description relate to the beta hCG-B11 conjugate disclosed in D1, but no conjugate containing an immunostimulatory agent as listed in claim 8 is disclosed. Therefore the subject-matter of present claims 1-30, if solving the problem of providing an alternative beta hCG-B11 conjugate, are arbitrary solutions not involving an inventive step.

The dependent claims 32, 33, 35, 36, 38 and 40 do not appear to contain any additional features which, in combination with the features of claim 31, involve an inventive step as the relevant subject matter is either arbitrary or falls within the knowledge and ability of the skilled person.

Claims 41-45 differ from D1, closest prior art, by the fact they relate to method of immunizing a subject comprising administering an immunostimulatory agent and a conjugate of an

antibody that binds to APCs linked to beta hCG. No particular effect has been associated with such a method. Claims 41-45 are therefore not involving an inventive step.

INDUSTRIAL APPLICABILITY

For the assessment of the present claims 41-45 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

The present application disclose a conjugate comprising a monoclonal antibody binding to APCs linked to beta human chorionic gonadotropin. However no conjugate containing a monoclonal antibody binding to APCs linked to beta human chorionic gonadotropin and to an immunostimulatory agent, as claimed or referred to in claims 1-30, 32, 33, 40 and 42 is disclosed. The present application therefore does not meet the requirement of Article 5 PCT stating that the application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Re Item VIII

Claims 16-18 are directed to a molecular conjugate comprising an antibody defined by the CDR3, the CDR2 or the CDR1 of the heavy and the light chains (claim 16-18, respectively) and conservative modifications thereof. The antigenic specificity of the antibodies is not defined. It is not sufficient to characterize an antibody with two of the CDR sequences since an antibody is structurally made of two light chains and two heavy chains, and the combination of them is necessary to confer antigen binding specificity. Claims 19 and 25 also define the antibody insufficiently. Claims 16-19 and 25 therefore do not clearly define the structure of

the antibodies and thus do not meet the requirements of Article 6 PCT.

The terms "conservative modifications thereof" used in claims 16-18 and "derived from" used in claims 19 and 25 are unclear and broaden the claims to include subject-matter not supported by the description, thereby contravening the requirements of Art. 6 PCT.

The terms "or an amino acid sequence that is sufficiently homologous to SEQ ID No:4 or SEQ ID No:8 such that the antibody retains the ability to bind to human dendritic cells" used in claim 20 and the terms " such that a T cell-mediated immune response is generated against the antigen" used in claim 27 are considered to define the claimed subject-matter in terms of result to be achieved instead of using technical features. Claims 20 and 27 therefore do not meet the requirements of Article 6 PCT.